REMARKS

Favorable consideration and allowance are respectfully requested for the claims of this application

The rejection of claim 39 under 35 U.S.C. 112, second paragraph, as indefinite, is respectfully traversed.

Claims 38-41 are amended to clarify that it is *either or both* of the at least one compound of group (i) *and* the at least one compound of group (ii) that is subject to the recited condition. In particular, the word "said" is inserted before the phrase "at least one compound selected from group (ii)" in each claim, and the visual arrangement of the claim language is now clarifies that the phrase "wherein one or more of" refers to both:

"said at least one compound selected from group (i)"

and

"said at least one compound selected from group (ii)".

For instance, claim 38 is properly read so that it is directed to all of the following possibilities

one or more compounds of group (i) are present in the form of a free base *and/or*

one or more compounds of group (ii) are present in the form of a free base.

Each of claims 38-41 are similarly amended, albeit the case that each of them is directed to a different recited condition. This language is believed to clarify what is claimed and thereby overcome the asserted definiteness issue. Reconsideration and withdrawal of this rejection are therefore respectfully requested.

The rejection of Claims 37, 48-51, 54, 57 and 71-73 under 35 U.S.C. 103(a) as obvious over the proposed combination of Chutka et al. ("Urinary Incontinence in the Elderly: Drug Treatment Options," 1998, Drugs, Volume 56, Number 4, Pages 587-595), in view of Buschmann (US Patent 5,811,582) and Andersson et al ("The pharmacological treatment of urinary incontinence," 1999, British

Journal of Urology International, 84:923-947) is respectfully traversed.

The claimed invention provide substance combinations which are useful to treat a patient suffering from an increased urge to urinate or urinary incontinence. These combinations exhibit analgesic action and also fewer side effects when compared with the previously known treatments. Further, the claimed combinations exhibit a synergistic effect in treating urinary incontinence (see, e.g., US 2004/0242617, [0010]) when compared with treatments involving administration of the active ingredients alone.

Surprisingly, it has been discovered that a combination of compounds of group (i) (opioids and other substances) and compounds of group (ii), (muscarine antagonists and other substances) together provide an excellent therapy for bladder function. This result is remarkable considering that the compounds of group (i) have a central action and can interact with opioid receptors, whereas the compounds of group (ii) are known to be active in urinary incontinence and have a predominantly peripheral action, (see, e.g., US 2004/0242617, [0011]).

The Chutka et al. article relates to drug treatment options for urinary incontinence in the elderly. The article states that both anticholinergic drugs and opioids can decrease the contraction of the detrusor by impairing the contractility of the detrusor and potentially lead to urinary retention (see, e.g., Chutka et al., p. 593, 3rd paragraph and Table 1).

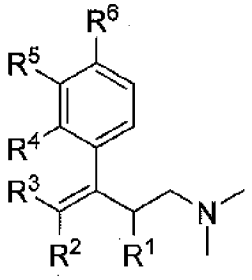
The Chutka et al. article is silent on the use of a <u>combination</u> of opioids and anticholinergic drugs (i.e. antimuscarinic drugs). Further, the articles does not teach or suggest that a combination of an opioid and an antimuscarinic drug would achieve anything other than an additive effect, let alone a synergistic effect as is shown in the present application (see, e.g., the text of the present application, p. 15, Example 1, in particular the table).

This table in the present application shows the results of a comparative study where (+)-(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-2-ol hydrochloride (as an exemplary compound from group (i)) and oxybutynin (as an exemplary compound from group (ii)) were administered to narcotic rats in

cystometric experiments. In particular, in this study the compounds were separately as well as in combination. The separate administration of each of the compounds from groups (i) and (ii) resulted in an inhibition of the rate of contractions of 21.7% and 10.7%, respectively. In contrast, administering a combination of compounds from groups (i) and (ii) yielded an inhibition of 42.5%. These results show a clear synergistic effect achieved by the combined administration of the compounds. This effect is not merely additive, as the sum of the two effects of compounds (i) and (ii) together would have resulted in an inhibition of only 32.4%. Thus, administration of the combined treatment is 31% more effective than the additive effects of the compounds which might otherwise have been expected based on their action when administered alone.[1]

As a result of this synergism achieved with the combination treatment, therapeutic results may be achieved with lower doses being administered. Because lower dosages can be utilized, the side effects which otherwise occur at higher dosages can be significantly reduced and perhaps even eliminated.

The '582 patent refers to dimethyl-(3-aryl-but-3-enyl)-amine compounds corresponding to formula I (shown below). These compounds are asserted to have an analgesic effect. The patent teaches that these compounds are suitable for the treatment of severe pain without giving rise to the typical side effects associated with opioids (see, e.g., '582 patent, col. 1, lines 6-8 and 46-50). According to the '582 patent some of the compounds have a greater analgesic effect than tramadol (see, e.g., '582 patent, col. 15, Table).



Formula I of the '582 patent

[1] (32.4 x 1.31 = 42.5)

The compounds taught in the '582 patent are structurally distinct from the compounds of group (i) (see groups a) to e)) of the present application. For instance, the compounds of the '582 patent all include a carbon to carbon double bond, which is not present in compound (i) of the present application (see the carbon atom adjacent the R^2 and R^3 subgroups in Formula I of the '582 patent).

The Office Action indicates that (2RS, 3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-2-ol hydrochloride (see, e.g., Example 1) would have a greater analgesic effect than tramadol. In the '582 patent, however, this compound is only taught as a precursor compound for the preparation of (Z)-(2RS, 3RS)-[3-(3-methoxyphenyl)-2-methyl-pent-3-enyl] dimethylamine (see, e.g., '582, Example 1). It is well settled that absent some indication or other teaching of a particular use for a chemical compound, a compound cannot serve as a suitable starting point as the basis for an obviousness rejection. The disclosre of the chemical intermediate without some indication of a particular use for the intermediate does not amount to a particular use for a compound that would permit the use of the intermediate to support an obviousness rejection. The '582 patent does not disclose any testing of this compound for analgesic properties. Not only does the '582 patent fail to teach or suggest that this compound might have some analgesic action, this compound is structurally dissimilar from the compounds of the present invention as this compound bears an alkene moiety.

Further, the '582 patent is silent on any treatment of an increased urge to urinate or urinary incontinence. Instead, the reference appears to be limited to treating severe pain.

Accordingly, the '582 patent provides no hint that any of the compounds of group (i) according to the present application would be suitable for treating any condition other than pain, let alone treating an increased urge to urinate or urinary incontinence. Additionally, there is no teaching or suggestion in the '582 patent that it would be beneficial to combine any of the compounds of group (i) according to the present application, with an antimuscarinic drug such that of the compounds of group (ii) for treating an increased urge to urinate or urinary

incontinence, let alone that such a combination would result in a synergistic effect.

The Andersson et al. article relates to treating urinary incontinence and states that antimuscarinic drugs such as atropine and oxybutynin are useful for such a treatment (see, e.g., Andersson et al., title; p. 924, Table 2; p. 925, 3rd paragraph).

The Andersson et al. article does not teach or suggest administering a combination of opioids and anticholinergic drugs (i.e. antimuscarinic drugs), let alone that a combination of an opioid and an antimuscarinic drug might result in a synergistic effect.

There is nothing in the cited references that would cause the skilled artisan to try a combination therapy as contemplated by the present claims. Accordingly, the skilled artisan would not have arrived at the presently claimed subject-matter based on the cited references. Even assuming, *arguendo*, that a skilled artisan, were, for some reason, inclined to try such a therapy, the unexpected synergistic effects achieved with the claimed invention are such an unexpected beneficial result that the invention cannot be considered obvious over the cited references. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of Claims 55 and 56 under 35 U.S.C. 103(a) as obvious over Chutka et al. ("Urinary Incontinence in the Elderly: Drug Treatment Options," 1998, Drugs, Volume 56, Number 4, Pages 587-595), in view of Buschmann (US Patent 5,811,582), Andersson et al ("The pharmacological treatment of urinary incontinence," 1999, British Journal of Urology International, 84:923-947 and cited by Applicant) and Buschmann et al. (US Patent 6,248,737) is respectfully traversed.

Claims 55 and 56 relate to the particular diastereomer or enantiomer or mixture thereof that is present as the compound from group (i).

The Chutka and Andersson articles are discussed above. The '737 patent teaches 1-phenyl-3-dimethylaminopropane compounds having a pharmacological effect and discloses (2RS,3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-2-ol hydrochloride (see, e.g., '727, title and p. 6, Examples 1 and 2) and furthermore teaches that the (+)-enantiomer of this compound has a greater analgesic effect that the (-)-enantiomer.

Although Examples 1 and 2 according to '737 patent are relevant to the compounds of group (i), in particular, group a) of the present invention, the '737 patent is silent on the use of these compounds for treating an increased urge to urinate or urinary incontinence. Instead, the '737 patent merely teaches treating severe pain.

Moreover, the present application discloses that when (+)-(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-2-ol hydrochloride is administered by itself to narcotic rats in a cystometric study an inhibition of the rate of contractions of 21.7% is achieved. In contrast, a combination of this enantiomer and Oxybutynin led to an inhibition of 42.5% (see, e.g., present application, p. 15, Example 1, in particular, the table).

There is nothing in the cited prior art that would cause a person skilled in the art to have expected such a synergistic effect, regardless of whether the references are considered individually or collectively.

Further, there is no hint in the '737 patent or the other cited references that any of the compounds of group (i) of the present application would be suitable for treating any condition other than pain, let alone treating an increased urge to urinate or urinary incontinence. Additionally, there is no hint in the '737 patent or the other cited references that compounds of group (i), either when taken alone or when combined with a compounds of group (ii) would be useful for treating an increased urge to urinate or urinary incontinence. And, as stated above, there is nothing to suggest the unexpected beneficial result achieved by the claimed combination of compounds as evidenced by the synergistic results presented in the present application.

The claimed combinations have proved to be active at low doses - significantly lower than those which might reasonably been expected. As a result, it is possible to administer the combined active compounds in a low dose and still achieve a pharmacologically effective result. Further, the side effects which would otherwise occur at higher dosages are significantly decreased or even eliminated, without any compromise in therapeutic effect. Thus, the claimed combination of compounds presents a significant and unexpected advance over the prior art. This improvement is not taught or suggested in the cited prior art.

In sum, the skilled artisan would not have had reason to try a combination of compounds as required of the present claims. For this reason, the presently claimed subject matter cannot be considered obvious based on the cited references. Moreover, the unexpected and surprising synergistic effects achieved by the claimed combination of compounds compel a conclusion that the claims are allowable over the cited references.

For these reasons, the obviousness rejection cannot be properly maintained and reconsideration and withdrawal thereof are respectfully requested.

CONCLUSION

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket No. 029310.53299US).

Respectfully submitted,

February 11, 2009

/Christopher T. McWhinney/

Christopher T. McWhinney
Registration No. 42,875

J. D. Evans
Registration No. 26,269

CROWELL & MORING, LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
CTM